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ORIGINAL ARTICLE

The use of D-glucose-based silyloxy dienes in anthracyclinone synthesis

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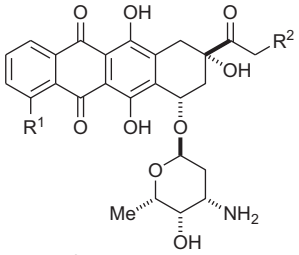
Asymmetric Diels–Alder reaction;
D-Glucose-based silyloxy dienes

Abstract We wish to report asymmetric Diels–Alder reactions using a D-glucose-based diene and quinol dienophile without requiring additional steps of preparing an oxirane dienophile typically used in the Stoodley group. A new D-glucose-based diene is also reported and its chemistry investigated.

1. Introduction

The anthracycline antibiotics, such as daunomycin (Daunoblastin®) **1**, doxorubicin (Adriablastin®) **2** and semi-synthetic idarubicin (Zavedos®) **3** are a widely-studied class of chemotherapeutic agents currently used in the treatment of a broad spectrum of solid tumours, lymphomas and leukaemias (Arcamone, 1981; Grynkiewicz et al., 2002; Monneret, 2001). Daunomycin **1** was originally isolated as a red-coloured metabolite from cultures of *Streptomyces peucetius* (Cassinelli and Orezzi, 1963). Although they are often used (as water soluble hydrochloride salts) in combination with other agents, they still present unpleasant side-effects (including cardio-toxicity and attack of the mucous membranes) and doxorubicin **2** activity can be impeded by the outgrowth of drug-resistant tumours (Priebe et al., 1998; Robinson et al., 1997).



1: R^1=OMe, R^2=H: Daunomycin
2: R^1=OMe, R^2=OH: Doxorubicin (Adriamycin)
3: R^1=H, R^2=H: Idarubicin

Their primary mode of interaction with tumour cells is by a process of intercalation (Chaires, 1998) into the major groove

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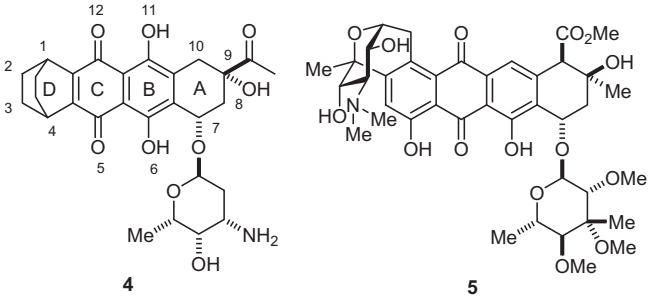
of nucleolar DNA and inhibition of the replication process (Fig. 1 which also includes a *spermine* ligand based on Dautant et al., 1995; key: carbon atom, grey; oxygen, red; nitrogen blue). The DNA base pairs above and below the drug 'buckle' in conformation to afford a distorted DNA helix (Frederick et al., 1990; Wang et al., 1987) thereby preventing correct association with the DNA helicase, topoisomerase II (Wang, 1996; Pommier, 1995) and polymerase families of enzymes to initiate DNA replication for RNA synthesis, protein formation and thereby cell division.

Also, the anthracyclines can cause DNA single-strand breaks by way of free radicals (Arcamone, 1981) and, therefore, cause irreversible damage. A few years ago, a group of synthesised alkylcyclines was reported with both DNA alkylating and intercalating properties (Geroni et al., 2001).

It was decided to prepare the previously unknown ring-D modified anthracycline **4** and to assess its anticancer activity as a more bulky ring-D would make intercalation more difficult and could prove whether intercalation is necessary for tumour growth inhibition. Indeed the more bulky bicyclic nogalamycin **5** intercalates (Smith et al., 1995) into DNA creating a more strained complex and shows anticancer activity.



Over the last several decades, syntheses of anthracyclinones and anthracyclines have been developed, initially creating racemic mixtures (Arcamone, 1981) and then focusing on stereoselective routes to enantiomerically pure anthracyclinones (Achmatowicz and Szechner, 2008).

Monosaccharides, such as D-glucose are used as chiral auxiliaries in organic synthesis (Tadano and Totani, 2008) and in this study it is attached to silyloxy dienes. Following Stoodley's chromatography-free synthesis of (+)-4-demethoxydaunomycinone (the aglycone of idarubicin) (Gupta et al., 1984), it was decided to follow a similar approach using a D-glucose-based silyloxy diene, based upon the asymmetric Diels–Alder reaction (Bañuelos et al., 2010; Nicolaou et al., 2002; Whiting, 1996) as shown in Scheme 1. Here, the electron-deficient oxirane **6** reacted with the electron-rich diene **7** to afford the cycloadduct **8** (60% diastereomeric excess) in 74% yield (Gupta et al., 1984). An analytical sample was obtained after two crystallisations. Enantiopure syntheses of several other anthracyclinones were subsequently reported (Bourghli and Stoodley, 2004; Edwards et al., 1991; Kotha and Stoodley, 2002) involving similar asymmetric Diels–Alder reactions.

In this article based upon the *Doctoral* thesis (Miller, 1994), part of the synthesis is reported directed towards the target anthracycline **4** and the preparation of a new D-glucose-based diene **21** and some of its chemistry investigated. The stereochemistry of the new compounds described in this study is from the model **14** described and by analogy to previously reported investigations (Gupta et al., 1984, 1988).

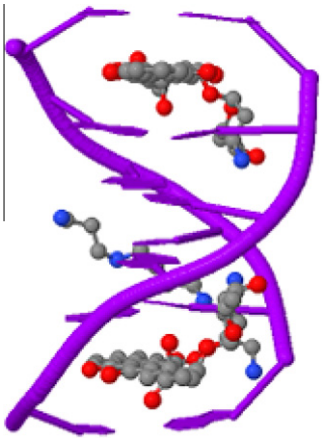
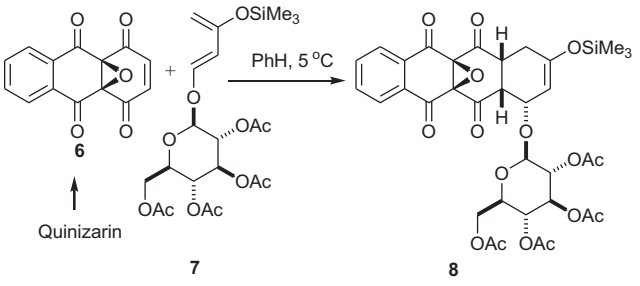


Figure 1 Intercalation of idarubicin **3** with D(CGATCG) fragment.

2. Experimental (materials and methods)

Ethyl acetate and hexanes were distilled prior to use. Dry solvents used in the experiments were prepared as follows: dichloromethane was distilled off calcium hydride or phosphorus(v) oxide and stored over 4Å molecular sieves; hexane was distilled off phosphorus(v) oxide; benzene and toluene were distilled off sodium benzophenone ketyl. Dry diethyl ether used for the trituations and crystallisations was prepared by allowing the solvent to stand over sodium wire for a minimum of one week. Deuteriochloroform, used as a solvent for the determination of NMR spectra, was stored over tin granules. TLC (Thin Layer Chromatography) was carried out on Merck plastic plates coated with silica gel (60 F_{254}). The plates were either observed under UV light (Mineralight UVG2-58 lamp) or developed with iodine vapour or a sulfuric acid stain (EtOH: conc. H_2SO_4: p-$MeOC_6H_4CHO$, 95:4:1). Column chromatography was performed under pressure (ca. 7×10^4 Pa) using either Merck Kieselgel H Type 60 or Crossfield Sorbsil C60 flash silica. Melting points were determined using a Büchi 512 melting point apparatus. Optical rotations, measured at *ca.* 20 °C using either a Thorn Type 243 or an Optical Activity 1000 polarimeter, are given in 10^{-1} deg cm^2 g^{-1}. IR spectra were recorded using a Perkin–Elmer 783 spectrometer using KBr discs. A Perkin–Elmer Lambda 15 was used to determine



Scheme 1 Asymmetric Diels–Alder reaction.

UV spectra; extinction coefficients (ε) are presented in $cm^2\ mmol^{-1}$. ^1H NMR spectra were measured at room temperature at 300 MHz using a Brucker AC 300 or a 220 MHz using a Perkin–Elmer spectrometer. A Kratos MS45 spectrometer was used to obtain EI and CI mass spectra (NH_3 as the carrier gas); FAB mass spectra (p-$NO_2C_6H_4CH_2OH$ as matrix) were measured using a Kratos Concept IS spectrometer. Elemental analyses were performed with a Carlo–Erba Model 1106 analyser.

*2.1. Preparation of 1,4,4a,9a-tetrahydro-5,8-dihydroxy-1,4-ethano-9,10-anthraquinone (**11**)*

To a solution of naphthazarin **10** (1.9 g, 10 mmol) in toluene (40 ml) cyclohexa-1,3-diene (2.43 g, 30.32 mmol) was added. The mixture was heated at reflux under argon for 3 days. After removal of the solvent and residual diene by evaporation, the crude cycloadduct **11** (2.62 g, 9.69 mmol, 97%) was obtained. Crystallisation from chloroform afforded the *title* compound **11** (1.67 g, 6.18 mmol, 62%) as a brown solid, m.p. 128–132 °C, IR(KBr): ν_{max} (cm^{-1}): 1620 (C═O) and 1580, λ_{max} (EtOH): 398 (ε 7700), 232 (16 300) and 213 (13 600) nm; ^1H NMR($CDCl_3$, 300 MHz): δ_H: 1.41–1.48 and 1.77–1.84 (each 2 H, m, CH_2CH_2), 3.19 (2 H, s, 4a- and 9a-H), 3.42 (2 H, br s, 1- and 4-H), 6.22 (2 H, dd, ^3J 4.5, ^3J 3 Hz, 2- and 3-H), 7.22 (2 H, s, 6- and 7-H) and 12.8 (2 H, s, 5- and 8-OH); EI-MS: m/z: 270 (M^+) 5% and 80, 100%; CI-MS: m/z: 271 (MH^+) 100%. *Anal.* Calc. for $C_{16}H_{14}O_4$: C, 71.1; H, 5.2. Found: C, 71.2; H, 5.2%.

*2.2. Preparation of 1,2,3,4,4a,9a-hexahydro-5,8-dihydroxy-1,4-ethano-9,10-anthraquinone (**12**)*

The cycloadduct **11** (0.305 g, 1.128 mmol) was stirred with 10% palladium on charcoal (0.15 g, 0.5 mass eq.) in dry dichloromethane (10 ml) under an atmosphere of hydrogen for 1 day (the reaction being monitored by 220 MHz ^1H NMR spectroscopy). After filtration through celite and removal of the solvent from the filtrate, the crude reduced product (0.28 g, 1.03 mmol, 91%) was obtained. Crystallisation from 1:1 chloroform-hexane afforded an analytical sample of *title* compound **12** (0.10 g, 0.367 mmol, 32.5%) as a light-yellow solid, m.p. 153-153.5 °C, IR(KBr): ν_{max} (cm^{-1}): 1610 (C═O); λ_{max} (EtOH): 398 (ε 7400), 256 (9200), 233 (16 100) and 212 (12 700) nm; ^1H NMR($CDCl_3$, 300 MHz): δ_H: 1.45 and 1.75 (each 4 H, br s, together CH_2CH_2), 2.39 (2 H, br s, 1- and 4-H), 3.12 (2 H, s, 4a- and 9a-H), 7.29 (2 H, s, 7- and 8-H) and 12.77 (2 H, s, 5- and 8-OH); EI-MS: m/z: 272 (M^+) 100% and 192, 92%; CI-MS: m/z: 273 (MH^+) 100% and 272 (M^+) 36%. *Anal.* Calc. for $C_{16}H_{16}O_4$: C, 70.6; 5.9. Found: C, 70.9; H, 5.7%.

*2.3. Preparation of 1,2,3,4-tetrahydro-5,8-dihydroxy-1,4-ethano-9,10-anthraquinone (**13**)*

A solution of compound **12** (4.28 g, 15.72 mmol) was warmed with 5 M sodium hydroxide (500 ml) in the presence of air for 6 h (the process being followed by TLC). Acidification at 0 °C with hydrochloric acid and filtration afforded a red solid. After washing with water and drying (P_2O_5; *in vacuo*), the quinol **13** was recovered (3.75 g, 13.87 mmol, 88%). An analytical sample (2.94 g, 10.9 mmol, 69%) was obtained by crystallisation from ethyl acetate to afford a red solid, m.p. 182–183 °C, IR(KBr): ν_{max} (cm^{-1}): 1610 (C═O) and 1570 (C═C); λ_{max} (EtOH): 549 (ε 4800), 518 (6900), 287 (7900) and 217 (31 000) nm; ^1H NMR($CDCl_3$, 300 MHz): δ_H: 1.35 and 1.81 (each 4 H, br d, separation 7 Hz, 2 × CH_2CH_2), 3.58 (2 H, br s, 1- and 4-H), 7.20 (2 H, s, 6- and 7-H) and 12.73 (2 H, s, 5- and 8-OH); EI-MS: m/z: 270 (M^+) 83% and 242 (M^+ -C_2H_4) 100%; CI-MS: m/z: 273 (MH_3^+) 100%. *Anal.* Calc. for $C_{16}H_{14}O_4$: C, 71.1; 5.2. Found: C, 70.8; H, 5.1%.

*2.4. Reaction of 1,2,3,4-tetrahydro-5,8-dihydroxy-1,4-ethano-9,10-anthraquinone (**13**) with the D-glucose-based diene (**14**)*

A solution of the quinol **13** (0.09 g, 0.333 mmol) and the D-glucose-based diene **14** (Larsen and Stoodley, 1989) (0.36 g, 0.680 mmol) in 'analar' toluene (8 ml) was refluxed under argon for 2.5 days. Removal of the solvent afforded a red-brown solid (0.46 g), which comprised of the cycloadduct **15** together with a trace of compound **16** and the glycoside **18** from its 300 MHz ^1H NMR spectrum. Subjection of this material to silica-gel chromatography [hexane-ethyl acetate (8:1–2:1) as eluant] afforded three fractions. The first-eluted material (0.015 g, 0.033 mmol, 10%) was *1,2,3,4-tetrahydro-5,12-dihydroxy-9-tert-butyldimethylsilyloxy-1,4-ethanonaphthacene-6,11-dione (**16**)*, m.p. 191–192 °C, IR(KBr): ν_{max} (cm^{-1}): 1750 and 1585 (C═O); λ_{max} (EtOH): 518 (ε 4800), 481 (7200), 268 (23 100), 232 (12 800), 214 (15 200) nm; ^1H NMR($CDCl_3$, 300 MHz): δ_H: 0.31 (6 H, s, Me_2Si), 1.02 (9 H, s, Me_3C), 1.39 and 1.85 (each 4 H, br d, separation 7 Hz, 2 × CH_2CH_2), 3.70 (2 H, br s, 1- and 4-H), 7.20 (1 H, dd, ^3J 8.5 Hz, 2.5 Hz, 8-H), 7.70 (1 H, d, ^3J 2.5 Hz, 7-H), 8.24 (1 H, d, ^3J 8.5 Hz, 10-H) and 13.35 & 13.52 (each 1 H, s, 5- and 12-OH); EI-MS: m/z: 450 (M^+) 100%, 383 (M^+–Me_3C) 79% and 338, 13%; CI-MS: (m/z): 451 (MH^+) 100%; FAB-MS: (m/z): 451 (MH^+) 100%. *Anal.* Calc. for $C_{26}H_{30}O_5Si$: C, 69.3; H, 6.7; Si, 6.2. Found: C, 69.0; H, 6.8; Si, 5.9%.

The second-eluted material (0.133 g, approx. 50% of **15**) was crystallised from chloroform-hexane followed by dichloromethane-hexane to give *(6aR,7S,10aR)-1,2,3,4,6a,7,10,10a-octahydro-5,12-dihydroxy-7-(2',3',4',6'-tetra-O-acetyl-β-D-glucopyranosyloxy)-9-tert-butyldimethylsilyloxy-1,4-ethanonaphthacene-6,11-dione (**15**)* (0.062 g, 0.077 mmol, 23%) as a pale-yellow solid, m.p. 179-180 °C, $[\alpha]_D$ + 281 (c 0.05% in CH_2Cl_2), IR(KBr): ν_{max} (cm^{-1}): 1750 (ester C═O) and 1670 (ketone C═O); λ_{max} (EtOH): 517 (180), 484 (275), 396 (9400), 273 (7300), 243 (24 300) and 205 (19 200) nm; ^1H NMR($CDCl_3$, 300 MHz): δ_H: 0.18 and 0.22 (each 3 H, s, Me_2Si), 0.95 (9 H, s, Me_3C), 1.29 and 1.47 (each 2 H, br d, separation 8 Hz, CH_2CH_2), 1.80 (4 H, br d, separation 9 Hz, CH_2CH_2), 1.73, 1.88, 1.97 and 2.09 (each 3 H, s, 4 × $MeCO_2$), 2.16 (1 H, dd, ^3J 18.5 Hz, ^3J 8 Hz, 10-H β), 3.1–3.2 (1 H, m, 6a-H), 3.38 (1 H, t, ^3J 7 Hz, 10a-H), 3.52–3.58 (1 H, m, 5′-H), 3.61-3.65 (each 1 H, br s, 1- and 4-H), 4.04 (1 H, dd, ^3J 12 Hz, ^3J 2.5 Hz, 6′-H), 4.17 (1 H, dd, ^3J 12 Hz, ^3J 4.5 Hz, 6′-H), 4.36-4.44 (2H, m, 1′- and 2′-H), 4.56 (1 H, t, ^3J 5 Hz, 7-H), 4.94-4.96 (2 H, m, 3′- and 4′-H), 5.15 (1 H, d, ^3J 4.5 Hz, 8-H), 11.66 and 12.28 (each 1 H, s, 5- and 12-OH)(irradiation at δ 4.56 caused the m at δ 3.1-3.2 to simplify and the d at δ 5.15 to collapse to a s); FAB-MS: m/z: 800 (M^+) 1.5%, 453 (M^+–$C_{14}H_{19}O_{10}$) 36% and 73, 100%. *Anal.* Calc. for $C_{40}H_{52}O_{15}Si$: C, 60.0; H, 6.6; Si, 3.5. Found: C, 59.2; H, 6.4; Si, 3.4%.

(b) A stirred solution of the quinol **13** (0.486 g, 1.8 mmol) and the D-glucose-based diene **14** (1.024 g, 1.93 mmol) in 'analar' toluene (30 ml) was heated at 98 °C under argon. The reaction was followed by 300 MHz ^{1}H NMR spectroscopy and, after 3 days, a further quantity of the diene (0.30 g, 0.57 mmol) dissolved in 'analar' toluene (30 ml) was added [to react with the unchanged quinol]. This mixture was heated at 98 °C for a further 24 h. Removal of the solvent *in vacuo* afforded mainly a 3:1 mixture of a 60% d.e. of the cycloadduct **15** and the quinol **13**, together with a trace of compound **16**. Crystallisation of the mixture from diethyl ether-hexane gave mainly the cycloadduct **15** (0.53 g, 0.66 mmol, 37%). Attempted recrystallisation of the impure cycloadduct **15** from diethyl ether-hexane gave an oil, which was subjected to silica-gel chromatography [hexane-EtOAc (8:1–1:1) as eluant].

The first eluted material (0.337 g) was observed as a 5.7:4:3.1 mixture of compounds **19**, the C-9 ketone and **15**. Recrystallisation of this mixture from dichloromethane-hexane afforded a mixture; its 300 MHz ^{1}H NMR revealed that partial hydrolysis (de-*O*-silylation) to the C-9 ketone had occurred. A final recrystallisation of this material afforded a yellow solid (0.165 g, 0.21 mmol, 11%) which contained a 11:2 mixture of *(6aR,7S,10aR)-1,2,3,4,6a,7,8,10a-octahydro-5,12-dihydroxy-(2',3',4',6'-tetra-O-acetyl-β-D-glucopyranosyloxy)-9-tert-butyldimethylsilyloxy-1,4-ethanonaphthacene-6,11-dione (**19**)* and the cycloadduct **15**, m.p. 177.5–179 C, $[\alpha]_D$ +231 (c 0.05% in CH_2Cl_2), IR(KBr): ν_{max} (cm^{-1}): 1750 (C═O); λ_{max} (EtOH): 517 (ε 5600), 483 (8800), 347 (10 100), 294 (4800), 274 (7500), 244 (25 800) and 205 (20 000) nm; for compound **(19)** ^{1}H NMR($CDCl_3$, 300 MHz): δ_H: 0.21 (6 H, s, Me_2Si), 0.93 (9 H, s, Me_3C), 1.31 and 1.38 (each 2 H, d, ^3J 9 Hz, ^3J 6.5 Hz, 2 × CH_2CH_2), 1.81 (4 H, d, ^3J 6.5 Hz, CH_2CH_2), 1.58, 1.89, 1.97 and 2.09 (each 3 H, s, 4 × $MeCO_2$), 2.41–2.61 (2 H, m, 8-Hα and 8-Hβ), 3.10 (1 H, dd, ^3J 9 Hz, ^3J 2 Hz, 6a-H), 3.54–3.60 (1 H, m, 5'-H), 3.64–3.66 (3 H, m, 1-, 4- and 10a-H), 4.05 (1 H, dd, ^3J 12 Hz, ^3J 2.5 Hz, 6'-H), 4.19 (1 H, dd, ^3J 12 Hz, ^3J 5 Hz, 6'-H), 4.41–4.47 (2 H, m, 7- and 1'-H), 4.58 (1 H, m, 2'-H), 4.94–4.97 (2 H, m, 3'- and 4'-H), 5.26 (1 H, dd, ^3J 5 Hz, ^3J 1.5 Hz, 10-H), 12.02 and 12.48 (each 1H, s, 5- and 12-OH) (irradiation at δ 3.10 caused the two br s at δ 3.6-3.64 to split into 3 signals and the m at δ 4.44 to simplify; irradiation of the m at δ 3.58 caused the dd at δ 4.02 and 4.18 to collapse to two d (^3J 12 Hz) and the m at δ 4.96 to simplify; irradiation of the m at δ 4.58 caused the m at δ 4.41–4.47 and 4.96 to simplify; irradiation at δ 5.26 caused the two br s at δ 3.6–3.64 to split into three signals and a minor change in the range δ 2.45–2.61); FAB-MS: (*m*/*z*): 800 (M^+) 18%, 743 (M^+–Me_3C) 1% and 453 (M^+–$C_{14}H_{19}O_{10}$) 100%. *Anal*. Calc. for $C_{40}H_{52}O_{15}Si$: C, 60.0; H, 6.6; Si, 3.5. Found: C, 60.0; H, 6.6; Si, 3.6%.

(c) To a stirred solution of the quinol **13** (0.013 g, 0.048 mmol), was added the D-glucose-based diene **14** (0.039 g, 0.073 mmol) and $Eu(fod)_3$ (0.002 g, 4 mol%) in 'analar' toluene (5 ml) and was heated at reflux under argon. After 2 days, a further quantity of the diene (0.017 g, 0.032 mmol) was added. Thus, after 4 h, a 1:1.1:1:0.4 ratio of compounds **13**, **15**, **14** and **16** was present; after 21 h, a 1:2.4:0.2:0.4 ratio of compounds **13**, **15**, **16** and **17** was detected; after 3 days only the aromatic compound **16** and the tetra-acetylglucose **17** were observed by 300 MHz ^{1}H NMR spectroscopy.

*2.5. Preparation of (E)-1-(2',3',4',6'-tetra-O-acetyl-β-D-glucopyranosyloxy)-3-triisopropylsilyloxybuta-1,3-diene (**21**)*

To a solution of the glycoside **18** (2.50 g, 6 mmol) and triethylamine (2.1 ml, 15 mmol) in dry dichloromethane (30 ml) was slowly added tri*iso*propylsilyl triflate (3.75 g, 12.2 mmol) at room temperature. An immediate darkening in colour was observed. After 70 min, triethylamine (3 ml, 21 mmol) and dichloromethane (30 ml) were added to the mixture, which was subsequently diluted with water. The organic phase was separated and washed with saturated aqueous sodium hydrogen carbonate, dried ($MgSO_4$) and evaporated to give a yellow oil. Trituration with dry diethyl ether and hexanes afforded the diene **21** (1.48 g, 2.58 mmol, 43%) as a cream solid, m.p. 51-52 °C, $[\alpha]_D$ −15 (c 0.6% in EtOH), IR(KBr): ν_{max} (cm^{-1}): 1760 (ester C═O), 1655 and 1640 (C═C); λ_{max} (EtOH) 240 (ε 14,200) nm; ^{1}H NMR($CDCl_3$, 300 MHz): δ_H: 1.10 (18 H, d, ^3J 6.5 Hz, 3 × Me_2CH), 1.21 (3 H, apparent heptet, separation 6.5 Hz, 3 × C*H*Me_2), 2.01, 2.03, 2.05 and 2.08 (3 H, s, 4 × $MeCO_2$), 3.80 (ddd, 1 H, ^3J 10 Hz, ^3J 5 Hz, ^3J 2 Hz, 5'-H), 4.10-4.15 (3 H, m, 4-H_2 and 6'-H), 4.24 (1 H, dd, ^3J 12.5 Hz, ^3J 5 Hz, 6'-H), 4.78 (1 H, d, ^3J 7.5 Hz, 1'-H), 5.11 (2 H, apparent t, separation 9.5 Hz, 2'- and 4'-H), 5.24 (1 H, t, ^3J 9.5 Hz, 3'-H), 5.65 (1 H, d, ^3J 12 Hz, 2-H) and 6.80 (1 H, d, ^3J 12 Hz, 1-H) ppm; FAB-MS: (*m*/*z*): 573 (MH^+), 15%, 331 ($C_{14}H_{19}O_9^+$) 76% and 169, 100%. Found: *M*H+, 573.2766. $C_{27}H_{44}O_{11}Si$ requires *m*/*z* 573.2731.

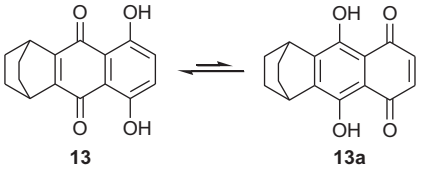
*2.6. Preparation of (1R,2R,3S)-3-(2'3'4'6'-tetra-O-acetyl-β-D-glucopyranosyloxy)-5-tri-isopropylsilyloxycyclohex-4-ene-1,2-N-phenyldicarboximide (**22**)*

A solution of the diene **21** (0.590 g, 1.03 mmol) and N-phenylmaleimide (0.174 g, 1.0 mmol) in dry benzene (5 ml) was left at room temperature for 1 day. Evaporation of the solvent left a residue, which, on the basis of 300 MHz ^{1}H NMR spectroscopy, comprised mainly an 85:15 mixture of the cycloadducts **22** and **24**. Trituration of the mixture with diethyl ether afforded the cycloadduct **22** (0.202 g, 0.26 mmol, 26%). An analytical sample was obtained by crystallisation from dry dichloromethane-dry diethyl ether-hexanes to afford the cycloadduct **22** (0.140 g, 0.18 mmol, 18%) as a pale-cream solid, m.p. 194–195 °C, $[\alpha]_D$ +51 (c 0.3%, CH_2Cl_2), IR (KBr): ν_{max} (cm^{-1}): 1760 (ester C═O), 1710 (imide C═O) and 1650 (C═C); λ_{max} (EtOH) 202 (ε 23 000) nm; ^{1}H NMR($CDCl_3$, 300 MHz): δ_H: 1.09 (18 H, d, ^3J 6.5 Hz, 3 × Me_2CH), 1.14–1.30 (3 H, m, 3 × C*H*Me_2), 1.53, 1.95, 2.00 and 2.08 (each 3 H, s, 4 × $MeCO_2$), 2.57 (1 H, dd, ^3J 16 Hz, ^3J 9.5 Hz, 6-Hα), 2.84 (1 H, dd, ^3J 16 Hz, ^3J 9 Hz, ^3J 2.5 Hz, 6-Hβ), 3.18 (1 H, dd, ^3J 10.5 Hz, ^3J 5 Hz, 2-H), 3.38 (1 H, apparent q, separation 10 Hz, 1-H), 3.60-3.65 (1 H, m, 5'-H), 4.03 (1 H, dd, ^3J 12.5 Hz, ^3J 2 Hz, 6'-H), 4.20 (1 H, dd, ^3J 12 Hz, ^3J 5 Hz, 6'-H), 4.63 (1 H, d, ^3J 8 Hz, 1'-H), 4.76–4.83 (2 H, m, 2'- and 3-H), 5.00 (1 H, t, ^3J 9.5 Hz, 4'-H), 5.12 (1 H, t, ^3J 9.5 Hz, 3'-H), 5.19 (1 H, dd, ^3J 7 Hz, ^3J 2 Hz, 4-H), 7.31-7.50 (5 H, m, Ph) ppm; FAB-MS: *m*/*z*: 768 (MNa$^+$) 4%, 746 (MH^+), 2%, 703 (M^+–C_3H_6), 7%, 702 (M^+–$CHMe_2$) 10%, 398 (M^+–$C_{14}H_{19}O_{10}^+$) 100%, 331 ($C_{14}H_{19}O_9^+$) 14% and 173, 49%. *Anal*. Calc. for $C_{37}H_{51}NO_{13}Si$: C, 59.6; H, 6.9; N, 1.9. Found: C, 59.3; H, 6.8; N, 1.9%.

3. Results and discussion

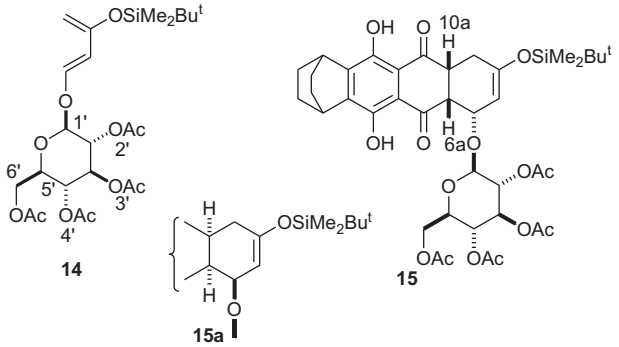
First of all the dienophile **13** was prepared as it is known that three-ringed dienophiles of this type tautomerise (Krohn and Tolkiehn, 1979) when undergoing the Diels–Alder reaction. This, therefore, avoids the extra steps in the preparation of a bicyclic oxirane analogue **20** of the dienophile **13** and removal of the oxirane functionality later on in the synthesis.

The previously unreported dienophile **13** was synthesised (Scheme 2) from commercially available naphthazarin **10** (Caygill et al., 2001) [see (Hout and Brassard, 1974; Lewis and Paul, 1977) for a multi-gram synthesis of **10**] in three steps and observed as a dark red solid in high yield from **10**. Its less stable tautomer (unobserved in the spectroscopic data) is represented below (structure **13a**).



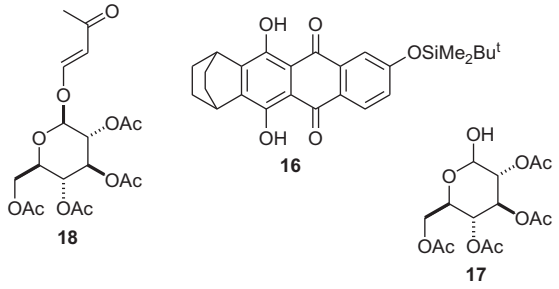
13 **13a**

We were now in a position to evaluate its reactivity with the D-glucose based diene **(**TBS-ether**; 14)** (Larsen and Stoodley, 1989), which proved to be more stable at higher temperatures than the diene **7**.



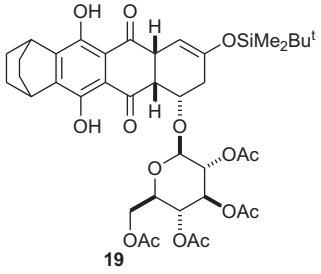
14 **15** **15a**

Different temperatures (from 0 °C to 160 °C) and solvents for the Diels–Alder reaction were investigated. Reaction of the quinol **13** with excess diene **14** in dry toluene at 98 °C afforded a 60% diastereomeric excess of the cycloadduct **15** after several days; the minor diastereomer **15a** detected in the ^{1}H NMR spectrum of the mixture had the opposite configuration at C-6a, C-7 and C-10a. The presence of the minor diastereomer of type **15a** was predicted by way of comparison to a previously reported investigation (Scheme 1) (Gupta et al., 1984) affording a 60% diastereomeric excess of cycloadduct **8** and by comparing the heights of the integrals of the 5- and 12-OH singlets of **15** and **15a**, respectively. Subjection of this mixture to silica-gel chromatography afforded the major diastereomer **15** (50% yield); an analytical sample (23% yield) was obtained after crystallisation. This cycloadduct possessed satisfactory spectroscopic data and use of the Karplus equation helped to determine to conformation of the ring-A by conversion of the vicinal coupling constants to torsional angles. Although the cycloadduct **15** is formed by heating the quinol **13** with the diene **14**, it is unstable at the temperature of refluxing toluene and undergoes some decomposition to a red solid **16** [an aromatic ring-A is created by elimination of the tetra acetyl-glucose **17**]. The diene **14** is unstable too and decomposes to the glycoside **18**.



18 **16** **17**

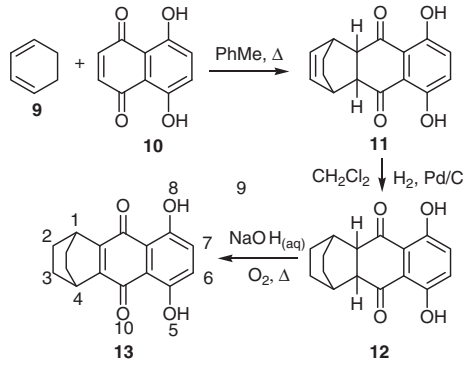
On a larger scale using similar reaction conditions, crystallisation of the resultant mixture from dry ether-hexane gave the crude cycloadduct **15** in approx. 37% yield based upon the quinol **13**. Further purification of compound **15** by silica-gel chromatography (ethyl acetate/hexane elution) and recrystallisation (chloroform/hexane) led to isomerisation of the double bond to positions 9,10 in ring-A, to afford predominantly the compound **19** (11% analytical yield) [11:2 mixture of compounds **19:15**].



19

In these diastereoselective Diels–Alder reactions, the dienophile tautomerises at elevated temperatures in order to allow the pericyclic reaction to occur at the C-6 and C-7 positions; no attachment of the diene at the C-4a and C-9a positions occurred.

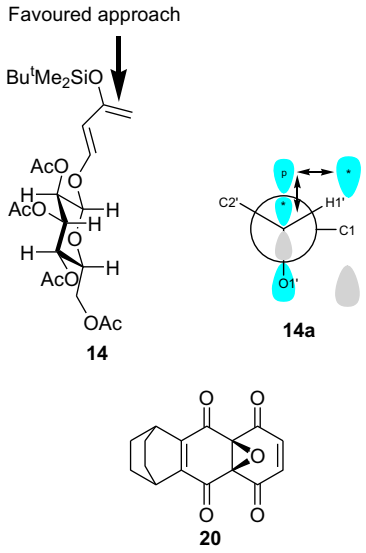
It was previously determined (Larsen and Stoodley, 1989) that the D-glucose based diene of type **14** exists in different conformations with regards to the diene moiety as based on the *exo*-anomeric effect (Gupta et al., 1989) in which the O-1



9 **10** **11** **12** **13**

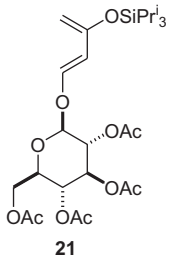
Scheme 2 Preparation of the dienophile **13**.

(between the diene and sugar) is sp^2 hybridised and its p-orbital overlaps with the π* antibonding orbital of the diene moiety and the σ* antibonding orbital as a result of the bond between C-1′ and O-1′ in **14a**; when O-1 is SP^3 hybridised (in C-1, O-1 saturated systems) there is a more favourable *gauche* (60°) relationship. The major cycloadduct formed results from *endo* top-side attack of the preferred conformation **14** by a dienophile, in the direction of the arrow, and the minor diastereomer from below the conjugated double bond. Obviously, the steric hindrance from the sugar reduces underside attack to lead to an approximate 60% diastereomeric excess of the major diastereomer.

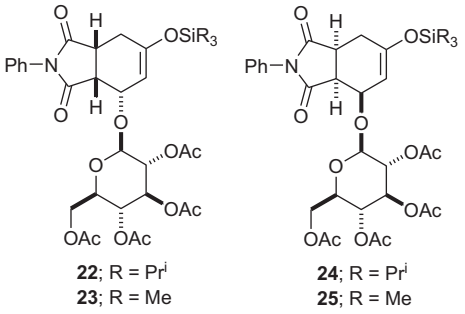


Clearly, using the quinol **13** as a dienophile avoids the unnecessary steps in synthesising the analogous oxirane of type **20** and later removal of the oxirane moiety, despite its slow reactivity and some thermal decomposition of the cycloadduct. The influence of a small amount the Eu(fod)$_3$ catalyst (Lowe and Stoodley, 1994) (lanthanide shift reagent) upon the reaction was studied under these conditions, on a very small scale, following its course by ^{1}H NMR spectroscopy. After 4 hours an equal amount of quinol **13** and cycloadduct **15** were detected; after 21 hours the ratio changed to 1:2.4, but unfortunately after 3 days only the aromatic material **16** and the tetraacetylglucose **17** were detected. The minor diastereomer of type **15a** was not detected in the mixture, so it is possible that the reaction was more diastereoselective and faster, but ultimately of little practical use.

With a view to developing a more efficient route, it was decided to prepare the glucose-based diene **21**. Hopefully it would be less prone to decomposition than its relatives **7** or **14**.



The glycoside **18** reacted with tri*iso*propyl triflate (Corey et al., 1981) in the presence of triethylamine to afford the *tri*isopropylsilyl-D-glucose-based diene **21** in 43% yield. The diene **21** showed the expected spectroscopic properties, albeit with a surprisingly low melting point.



It was of interest to compare the reactivity and diastereofacial selectivity of the dienes **7** and **21** with N-phenylmaleimide. Thus, in benzene at room temperature, the diene **21** reacted with N-phenylmaleimide to give predominantly a 85:15 mixture of the cycloadducts **22** and **24** by 300 MHz ^{1}H NMR spectroscopy, which after trituration with ether afforded the cycloadduct **22** in 26% yield. Crystallisation produced an analytical sample in 18% yield. Previously, the diene **7** had been shown (Gupta et al., 1988) to give a 86:14 mixture of the cycloadducts **23** and **25** and to afford after trituration and crystallisation the major compound **23** in 52% yield. Spectroscopic and microanalytical data were consistent for the cycloadduct **22**. Hydrolysis (de-*O*-silylation) of the cycloadduct **22** in acidified (0.1 M HCl) THF afforded (Miller, 1994) the C-5 ketone, which is a known compound (Gupta et al., 1988). Unfortunately, the reactivity of the diene **21** towards the quinol **13** was poor in toluene at 98 °C even in the presence of Eu(fod)$_3$. Further steps towards the synthesis of the anthracycline **4** via the de-*O*-silylated C-9 ketone have been previously reported in the *Doctoral* thesis (Miller, 1994).

4. Conclusions

The D-glucose-based diene of type **14** has reacted with the novel quinol **13** to afford a cycloadduct **15** (50%) with moderately high diastereoselectivity although the cycloadduct **15** has been found to be unstable under certain conditions and prone to thermolysis or isomerisation. Also, the previously unreported D-glucose-based silyloxy diene **21** has been found to undergo Diels–Alder reactions in a similar manner to the known dienes **7** and **14** and could be used in synthesis. D-glucose-based silyloxy dienes can also be unstable upon heating (e.g., 98 °C) for prolonged periods during a reaction.

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Perkins for mass spectral determinations and Dr. R. Perry for the elemental analyses.

References

Achmatowicz, O., Szechner, B., 2008. Synthesis of enantiomerically pure anthracyclinones. In: Krohn, K. (Ed.), . In: Topics in Current Chemistry: Anthracycline Chemistry and Biology I, vol. 282. Springer, Berlin, pp. 143–186.

Arcamone, F., 1981. Doxorubicin Anticancer Antibiotics. Academic Press, New York.

Bañuelos, P., García, J.M., Gómez-Bengoa, E., Herrero, A., Odriozola, J.M., Oiarbide, M., Palomo, C., Razkin, J., 2010. (1R)-(+)-Camphor and acetone derived α′-hydroxy enones in asymmetric Diels–Alder reaction: catalytic activation by Lewis and Brønsted acids, substrate scope, applications in syntheses, and mechanistic studies. J. Org. Chem. 75, 1458–1473.

Bourghli, L.M.S., Stoodley, R.J., 2004. Enantioselective synthesis of (+)-8-hydroxy-8-methylidarubicinone. Bioorg. Med. Chem. 12, 2863–2866.

Cassinelli, G., Orezzi, P., 1963. Daunomycin: a new antibiotic with cytostatic activity; isolation and properties. Giorn. Microbiol. 11, 167–174.

Caygill, G.B., Larsen, D.S., Brooker, S., 2001. Total synthesis of (+)-hatomarubigin. B. J. Org. Chem. 66, 7427–7431.

Chaires, J.B., 1998. Drug-DNA interaction. Curr. Opin. Struct. Biol. 8, 314–320.

Corey, E.J., Cho, H., Rücker, C., Hua, D.H., 1981. Studies with trialkylsilyltriflates: new syntheses and applications. Tetrahedron Lett. 22, 3455–3458.

Dautant, A., Langlois d'Estaintot, B., Gallois, B., Brown, T., Hunter, W.N., 1995. A trigonal form of the idarubicin:d(CGATCG) complex; crystal and molecular structure at 2.0 Å resolution. Nucleic Acids Res. 23, 1710–1716.

Edwards, W.D., Gupta, R.C., Raynor, C.M., Stoodley, R.J., 1991. Studies related to anthracyclines. Part 3. Stereoselective synthesis of (+)-daunomycinone. J. Chem. Soc., Perkin. Trans. 1, 1913–1918.

Frederick, C.A., Williams, L.D., Ughetto, G., van der Marel, G.A., van Boom, J.H., Rich, A., Wang, A.H.-J., 1990. Structural comparison of anticancer drug-DNA complexes: adriamycin and daunomycin. Biochemistry 29, 2538–2549.

Geroni, C., Ripamonti, M., Arrigoni, C., Fiorentini, F., Capolongo, L., Moneta, D., Marchini, S., Torre, P.D., Albanese, C., Lamparelli, M.G., Ciomei, M., Rossi, R., Caruso, M., 2001. Pharmacological and toxicological aspects of 4-demethoxy-3-deamino-3-aziridinyl-4′-methylsulphonyl-daunorubicin (PNU-159548): a novel antineoplastic agent. Cancer Res. 61, 1983–1990.

Grynkiewicz, G., Achmatowicz, O., Fokt, I., Priebe, W., Ramza, J., Szechner, B., Szeja, W., 2002. Syntezy naturalnych i modyfikowanych antybiotykow antracyklinowych ze wspolnego prekursora. Wiadomości Chemiczne 56, 535–560.

Gupta, R.C., Harland, P.A., Stoodley, R.J., 1984. An efficient enantiocontrolled synthesis of (+)-4-demethoxydaunomycinone. Tetrahedron 40, 4657–4667.

Gupta, R.C., Raynor, C.M., Stoodley, R.J., Slawin, A.M.Z., Williams, D.J., 1988. Asymmetric Diels–Alder reactions. Part 1. Diastereofacial reactivity of (E)-3-trimethylsilyloxybutyl-1,3-dienyl 2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranoside towards cyclic dienophiles. J. Chem. Soc., Perkin Trans. 1, 1773–1785.

Gupta, R.C., Larsen, D.S., Stoodley, R.J., Slawin, A.M.Z., Williams, D.J., 1989. Asymmetric Diels–Alder reactions. Part 2. A model to account for the diastereofacial reactivity of (E)-1-(2′,3′,4′,6′-tetra-*O*-acetyl-β-D-glucopyranosyloxy)-3-trimethylsiloxybuta-1,3-diene and its 2-methyl derivative. X-ray molecular structure of (E)-1-(2′,3′,4′,6′-tetra-*O*-acetyl-β-D-glucopyranosyloxy)-3-trimethylsiloxybuta-1,3-diene and of (1R, 6R, 9R, 10S)-9-Methyl-10-(2′,3′,4′,6′-tetra-*O*-acetyl-β-D-glucopyranosyloxy)bicyclo[4.4.0]dec-3-ene-2,5,8-trione. J. Chem. Soc., Perkin Trans. 1, 739–749.

Hout, R., Brassard, P., 1974. Friedel–Crafts condensations with maleic anhydrides. III. The synthesis of polyhydroxylated naphthoquinones. Can. J. Chem. 52, 838–842.

Kotha, S., Stoodley, R.J., 2002. Enantioselective synthesis of (+)-4-demethoxy-1,4-dimethyldaunomycinone. Bioorg. Med. Chem. 10, 621–624.

Krohn, K., Tolkiehn, H., 1979. Synthetische anthracyclinone, VIII(1) totalsynthese des daunomycinons. Chem. Ber. 112, 3453–3471.

Larsen, D.S., Stoodley, R.J., 1989. Asymmetric Diels–Alder reactions. Part 3. Influence of butadiene structure upon the diastereofacial reactivity of (E)-1-(2′,3′,4′,6′-tetra-*O*-acetyl-β-D-glucopyranosyloxy)buta-1,3-dienes. J. Chem. Soc., Perkin Trans. 1, 1841–1852.

Lewis, J.R., Paul, J., 1977. A convergent synthesis of naphthazarin and naphthopurpurin. Z. Naturforsch. 32b, 1473–1475.

Lowe, R.F., Stoodley, R.J., 1994. Hetero Diels–Alder reaction involving (E)-3-(tert-butyldimethylsiloxy)-1-(2′,3′,4′,6′-tetra-*O*-acetyl-β-D-glucopyranosyloxy)buta-1,3-diene and *p*-nitrobenzaldehyde. Tetrahedron Lett. 35, 6351–6354.

Miller, J.P., 1994. Asymmetric Synthesis of Anticancer Anthracyclines. Doctoral Thesis. University of Manchester.

Monneret, C., 2001. Recent developments in the field of antitumour anthracyclines. Eur. J. Med. Chem. 36, 483–493.

Nicolaou, K.C., Snyder, S.A., Montagnon, T., Vassilikogiannakis, G., 2002. The Diels–Alder reaction in total synthesis. Angew. Chem., Int. Ed. Engl. 41, 1668–1698.

Pommier, Y., 1995. DNA topoisomerases and their inhibition by anthracyclines. In: Priebe, W. (Ed.), Anthracycline Antibiotics – New Analogues, Methods of Delivery and Mechanisms of Action. ACS Symposium Series, vol. 574. Washington DC, pp. 183–203.

Priebe, W., Krawczyk, M., Kuo, M.T., Yamane, Y., Savaraj, N., Ishikawa, T., 1998. Doxorubicin- and daunorubicin–glutathione conjugates, but not unconjugated drugs, competitively inhibit C4 transport mediated by MRP/GS-X pump. Biochem. Biophy. Res. Commun. 247, 859–863.

Robinson, H., Priebe, W., Chaires, J.B., Wang, A.H.-J., 1997. Binding of two novel bisdaunorubicins to DNA studied by NMR spectroscopy. Biochemistry 36, 8663–8770.

Smith, C.K., Davies, G.J., Dodson, E.J., Moore, M.H., 1995. DNA-nogalamycin interactions: the crystal structure of d(TGATCA) complexed with nogalamycin. Biochemistry 34, 415–425.

Tadano, K., Totani, K., 2008. Monosaccharides as chiral auxiliaries and ligands for asymmetric synthesis. In: Fraser-Reid, O., Tatsuta, K., Thiem, J. (Eds.), Glycoscience. Springer, Berlin, pp. 1029–1075.

Wang, A.H.-J., Ughetto, G., Quigley, G.J., Rich, A., 1987. Interactions between an anthracycline antibiotic and DNA: molecular structure of daunomycin complexed to d(CpGpTpApCpG) at 1.2-Å resolution. Biochemistry 26, 1152–1163.

Wang, J.C., 1996. DNA topoisomerases. Annu. Rev. Biochem. 65, 635–692.

Whiting, A., 1996. Asymmetric Diels–Alder reactions. In: Stephenson, G.R. (Ed.), Advanced Asymmetric Synthesis. Chapman and Hall, London, pp. 126–145.